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Novel three-day community-based, non-pharmacological, group intervention for chronic musculoskeletal pain (COPERS): a randomized clinical trial.

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Abstract:	Background Chronic musculoskeletal pain is the leading cause of disability worldwide. The effectiveness of pharmacological treatments for chronic pain is often limited and there is growing concern about adverse effects, including opioid dependence. Non-pharmacological approaches to chronic pain may be an attractive alternative or adjunctive treatment. We describe the effectiveness of a novel, theoretically-based, group pain management support intervention for chronic musculoskeletal pain. Methods and findings We conducted a multi-centre, pragmatic, randomized controlled effectiveness and cost-effectiveness (cost utility) trial across 27 general practices and community musculoskeletal services in the UK. We recruited 703 adults with musculoskeletal pain of at least 3 months duration between August 2011 and July 2012 and randomized, 1.33:1, to intervention (403) or control (300). Intervention participants were offered a participative, group intervention (COPERS) delivered over 3 alternate days with a

	follow up session at 2 weeks. The intervention introduced cognitive behavioural approaches and was designed to promote self-efficacy to manage chronic pain. Controls received usual care and a relaxation CD. The primary outcome was pain related disability at 12 months (Chronic Pain Grade, CPG, disability subscale); secondary outcomes, measured at 6 and 12 months, included: Hospital Anxiety and Depression Scale (HADS) scores, Chronic Pain Acceptance Questionnaire; Health education impact Questionnaire Social integration subscale; Pain Self-Efficacy Questionnaire; pain intensity (CPG subscale), the Census global health question, health utility (EQ-5D-3L) and healthcare resource use. Analyses followed intention to treat principles, accounted for clustering by course in the intervention arm, and used multiple imputation for missing, or incomplete, primary outcome data. The mean age of participants was 59.9 years with: 81% white, 67% female, 23% in employment, 85% with pain for at least three years, 23% on strong opioids. Symptoms of depression and anxiety were common (baseline mean HADS scores 7.4 (SD 4.1) and 9.2 (4.6), respectively). Overall 282 (70%) intervention participants met the pre-defined intervention adherence criterion. Primary outcome data were obtained from 88% of participants. There was no significant difference between groups in: pain related disability at six or 12 months (12 months: difference -1.0, intervention vs. control, 95% CI -4.9 to 3.0); pain intensity; or the global health question. Anxiety, depression, pain self-efficacy, pain acceptance and social integration were better in the intervention group at six months; at 12 months these differences only remained statistically significant for depression (-0.7, 95% CI -1.2 to -0.2) and social integration (0.8, 95% CI 10.4 to 1.2). Intervention participants received more analgesics than the controls across 12 months. The total cost of the course per person was £145 ($214). The cost utility analysis showed there to be a small benefit in terms of QALYs (0.0325, 95% CI: -0.0074 to 0.0724), and on the cost side the intervention was a little more expensive (i.e. £188 ($277), 95% CI -£125 (-$184) to £501 ($738)), resulting in an ICER of £5,786 ($8,521) per QALY. Limitations include the fact that the intervention was relatively brief and did not include any physical activity components. Conclusions While the COPERS intervention is brief, safe and inexpensive with a low attrition rate, it was not effective for reducing pain related disability over 12 months (primary outcome). For secondary outcomes, we found sustained benefits on depression and social integration at 6 and 12 months, but there was no effect on anxiety, pain-related self-efficacy, pain acceptance, pain intensity or the census global health question at 12 months. There was some evidence that the intervention may be cost-effective based on a modest benefit on QALYs between groups. Trial registration International Standard Randomised Controlled Trial Number Register (ISRCTN) registration number 24426731, http://www.controlled-trials.com/isrctn/
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Novel three-day community-based, non-pharmacological, group intervention for chronic musculoskeletal pain (COPERS): a randomised clinical trial

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ABSTRACT

Background

Chronic musculoskeletal pain is the leading cause of disability worldwide. The effectiveness of pharmacological treatments for chronic pain is often limited and there is growing concern about adverse effects, including opioid dependence. Non-pharmacological approaches to chronic pain may be an attractive alternative or adjunctive treatment. We describe the effectiveness of a novel, theoretically-based, group pain management support intervention for chronic musculoskeletal pain.

Methods and findings

We conducted a multi-centre, pragmatic, randomized controlled effectiveness and cost-effectiveness (cost utility) trial across 27 general practices and community musculoskeletal services in the UK. We recruited 703 adults with musculoskeletal pain of at least 3 months duration between August 2011 and July 2012 and randomized, 1.33:1, to intervention (403) or control (300). Intervention participants were offered a participative, group intervention (COPERS) delivered over 3 alternate days with a follow up session at 2 weeks. The intervention introduced cognitive behavioural approaches and was designed to promote self-efficacy to manage chronic pain. Controls received usual care and a relaxation CD. The primary outcome was pain related disability at 12 months (Chronic Pain Grade, CPG, disability subscale); secondary outcomes, measured at 6 and 12 months, included: Hospital Anxiety and Depression Scale (HADS) scores, Chronic Pain Acceptance Questionnaire; Health education impact Questionnaire Social integration subscale; Pain Self-Efficacy Questionnaire; pain intensity (CPG subscale), the Census global health question, health utility (EQ-5D-3L) and healthcare resource use. Analyses followed intention to treat principles, accounted for clustering by course in the intervention arm, and used multiple imputation for missing, or incomplete, primary outcome data.

The mean age of participants was 59.9 years with: 81% white, 67% female, 23% in employment, 85% with pain for at least three years, 23% on strong opioids. Symptoms of depression and anxiety were common

(baseline mean HADS scores 7.4 (SD 4.1) and 9.2 (4.6), respectively). Overall 282 (70%) intervention participants met the pre-defined intervention adherence criterion. Primary outcome data were obtained from 88% of participants. There was no significant difference between groups in: pain related disability at six or 12 months (12 months: difference -1.0, intervention vs. control, 95% CI -4.9 to 3.0); pain intensity; or the global health question. Anxiety, depression, pain self-efficacy, pain acceptance and social integration were better in the intervention group at six months; at 12 months these differences only remained statistically significant for depression (-0.7, 95% CI -1.2 to -0.2) and social integration (0.8, 95% CI 10.4 to 1.2). Intervention participants received more analgesics than the controls across 12 months. The total cost of the course per person was £145 ($214). The cost utility analysis showed there to be a small benefit in terms of QALYs (0.0325, 95% CI: -0.0074 to 0.0724), and on the cost side the intervention was a little more expensive (i.e. £188 ($277), 95% CI -£125 (-$184) to £501 ($738)), resulting in an ICER of £5,786 ($8,521) per QALY. Limitations include the fact that the intervention was relatively brief and did not include any physical activity components.

Conclusions

While the COPERS intervention is brief, safe and inexpensive with a low attrition rate, it was not effective for reducing pain related disability over 12 months (primary outcome). For secondary outcomes, we found sustained benefits on depression and social integration at 6 and 12 months, but there was no effect on anxiety, pain-related self-efficacy, pain acceptance, pain intensity or the census global health question at 12 months. There was some evidence that the intervention may be cost-effective based on a modest benefit on QALYs between groups.

Trial registration International Standard Randomised Controlled Trial Number Register (ISRCTN) registration number 24426731, http://www.controlled-trials.com/isrctn/

Author Summary

Why Was This Study Done?

- Chronic pain, of which chronic musculoskeletal pain is a major component, is one of the most important causes of disability worldwide.
- Pharmacological interventions are ineffective, or only partially effective, for many people with chronic pain and there is increasing concern about side effects (for example with non-steroidal anti-inflammatory drugs) or drug dependence (with opioids or the gabapentinoids).
- After systematically reviewing the evidence we developed "COPERS" - a novel, brief, psychologically based, group intervention directed at increasing participants' confidence and their repertoire of skills around managing pain.
- Our aim was to reduce participants' pain related disability.

What Did the Researchers Do and Find?

- We conducted a large randomized control trial of the intervention; 703 participants, mostly identified from primary care, were randomized in a ratio of 1.33:1, to receive either the new intervention or usual care and a relaxation CD.
- We followed up participants from baseline (before they were allocated to a study arm) for 12 months and measured their pain related disability (our primary outcome) and a number of other secondary outcomes, including anxiety and depression and the amount of health care resources they used across the 12 months.
- The average age of the study participants was 60 years, few were in work and most (85%) had had pain for at least three years; overall at baseline they reported poor health and high levels of pain related disability, nearly a quarter (23%) were being prescribed strong opioids.
- The intervention had no effect on our primary outcome, pain related disability, at six or 12 months follow up. The psychological outcomes were better in the group receiving the intervention

compared to the usual care group at six months, but by 12 months only depression and social integration remained improved.

What Do These Findings Mean?

- This study suggests that brief, group based psychological interventions are insufficient to improve pain related disability in with people with long-established, chronic musculoskeletal pain and alternative treatments are needed.
- Anxiety and depression are common in people who have chronic pain and the study holds out the tantalising prospect that the new intervention could improve their psychological well-being, but further research is needed before this conclusion can be firmly drawn.

Introduction

Chronic pain is common, affecting an estimated 20% [1] to 30% [2] of adults worldwide. It is associated with disability, psychological co-morbidity, reduced quality of life, early mortality and high healthcare costs. The burden of disability due to chronic musculoskeletal disorders, commonly associated with chronic pain, increased worldwide by 46% between 1990 and 2010, with further increases predicted in coming years due to aging populations and increasing obesity [3]. In 2013 musculoskeletal disorders (combined with fractures and soft tissue injuries) accounted for over 20% of years lived with a disability across the globe [4]. Low back pain alone is the leading cause of disability in 86 countries and the second or third leading cause of disability in a further 67 countries [4].

Although pharmacological therapies have an important role in chronic pain, their effectiveness is often limited [5] and there is considerable concern about the adverse effects of non-steroidal anti-inflammatory drugs [6,7]. Many patients with chronic pain receive opioids, despite a lack of evidence around their long term effectiveness [8] and the risk of side-effects, including dependence [9].Non-pharmacological approaches to chronic pain, such as pain management and self-management support courses that aim to improve quality of life and encourage positive behaviour change, may be an attractive alternative. There are, however, limited data to support their use. There is evidence suggesting that improving self-efficacy (an individual's belief in their ability to succeed in a particular situation) may be a key mechanism for improvement in other outcomes [10,11] placing self-efficacy as a focus of interest for self-management interventions [12].

Based on a systematic review analysing the literature on the characteristics and effectiveness of pain management programmes [13], we developed a novel, theoretically underpinned, self-management support programme to improve the management of chronic musculoskeletal pain in the community and conducted a trial of this intervention: Coping with persistent Pain, Effectiveness Research into Self-management study (COPERS) [14]. This programme aimed to increase self-efficacy to manage chronic pain and attempted to

address the social isolation which may accompany the experience of living with chronic pain [14]. We conceptualised the intervention within the 'three-process model of pain' [15], which focuses on physiological processes, subjective-affective-cognitive processes, and behavioural processes. In this model these are non-discrete, interactive processes. Hence our intervention relied on changes in understanding, mood and behaviour to enhance pain-related self-efficacy, which in turn would interact to reinforce new behaviours and impact on outcomes. We hypothesised that this new intervention would reduce pain related disability in people with chronic musculoskeletal pain. Here we describe a randomised controlled trial testing the effectiveness and cost effectiveness of the COPERS programme.

Ethics Statement:

The trial was overseen by independent Trial Steering and Data Monitoring and Ethics committees. Ethical approval was granted by Cambridgeshire Ethics Committee Ref: 11/EE/046.

Methods

Study participants

We conducted a pragmatic, multi-centre, randomised controlled trial of the 'COPERS' group self-management course for adults living with chronic musculoskeletal pain. Causes of pain included, but were not restricted to, osteoarthritis, back pain, chronic widespread pain and fibromyalgia. Participants were recruited in the UK (London and the Midlands) from primary care, community musculoskeletal pain services and secondary care pain services. The trial protocol and statistical analysis plan have been published previously [16,17].

Between August 2011 and July 2012 Potential participants were identified via electronic patient record searches [18], face to face consultation, and advertisements in clinic areas. Those who responded to initial approaches or advertisement were sent a screening questionnaire. Eligibility was subsequently confirmed in a telephone interview with a researcher, who then sent potential participants a baseline questionnaire and consent form. We included adults (aged ≥ 18 years) with musculoskeletal pain of at least three months

duration [19]. Exclusion criteria were: inability to give informed consent; not fluent in English; chronic pain arising from active malignant disease or inflammatory arthritis; terminal illness; or such serious uncontrolled mental health or substance abuse issues that it would be difficult for the individual to participate in the group sessions (this was determined by the participant's general (family) practitioner (GP) following the electronic patient searches or at discussion between participant and researcher at the telephone interview). The trial was overseen by independent Trial Steering and Data Monitoring and Ethics committees (See Section 1 of S1 Appendix). Ethical approval was granted by Cambridgeshire Ethics Committee Ref: 11/EE/046.

Randomisation

Following the return of completed baseline questionnaires, participants were randomised to the two groups in a 1.33 to 1 ratio in favour of the intervention arm. Strict allocation concealment was maintained via an independent, centralised, online service which used stratified permuted blocks with randomly varying block sizes of 7 or 14 and recruitment site as a stratification factor.

Outcome Measures

Participants completed postal questionnaires containing the outcome measures before randomisation and at six and 12 months following randomisation. If necessary we collected primary outcomes by phone. Selection of outcome measures was based on their clinimetric qualities and informed by patient consultation. The primary outcome was pain related disability at 12 months. We chose a well-validated tool, the Chronic Pain Grade (CPG) which has two constructs—pain intensity and pain-related disability, which are scored independently and can be combined to form the Chronic Pain Grade [20]. Each construct has been validated separately [21]. The three disability subscale questions ask about pain interference with daily activities, change in ability to take part in recreational, social and family activities, and change in ability to work (including housework) over the past six months [20,21]. To generate the outcome each item is scored on a scale 0-10 (worst) and the mean is taken and multiplied by 100. This outcome has been used in a

number of other trials investigating long term pain [22,23]. Secondary outcomes were: the CPG pain intensity subscale [20,21], the census global health question [24], anxiety and depression (Hospital Anxiety and Depression Scale, HADS) [25], the Chronic Pain Acceptance Questionnaire (CPAQ) [26], the Health Education Impact Questionnaire (heiQ) Social integration and support subscale [27], health utility EQ-5D-3L [28], the Pain Self-Efficacy Questionnaire (PSEQ) [29]and health care resource use. We also examined use of psychotropic medicines, analgesics and weak and strong opioids by looking at total World Health Organisation defined daily doses (DDDs) of selected medications prescribed in the 12 months following randomisation and the proportion of participants using strong and weak opioids at 12 months follow up, full details of our outcome measures and methods are described in Sections 2, 3 and 4 of S1 Appendix. Due to the nature of the intervention, it was not feasible to mask participants or group facilitators to study arm. Participants' healthcare professionals and all those retrieving, handling or processing outcome data remained unaware of participants' allocated study arms.

Adverse events for both arms were collected following standard operation procedures for the Pragmatic Clinical Trials Unit and our adverse events protocol. Adverse events in the control arm could be reported by participants at any time via phone or post and we also collected all medical records at the end of the study. All deaths occurring during the study period were scrutinised to determine if they were related to the study.

Intervention

The intervention was a group facilitated, experiential learning course based on cognitive behavioural principles plus usual care (Table 1); its development and content is described in detail elsewhere [14]. Briefly, the course consisted of 24 individual components delivered in a community setting over three alternate days in one week with a follow-up session two weeks later (total duration = 14 hours). Content included: cognitive behavioural approaches to managing chronic pain (these covered: acceptance, attention control, goal setting and action planning, recognising unhelpful thinking and behaviours); an educational DVD with a pain consultant answering common questions from a patient with chronic pain; communication

skills; relationships; hobbies and activities; posture and movement; breathing, relaxation and guided imagery. Courses were delivered by two facilitators: a health care professional with experience of treating people with chronic musculoskeletal pain (physiotherapist, psychologist, osteopath, or GP) and a lay person living with chronic pain. Following a two day joint training programme, facilitators who met pre-determined competence criteria were selected to deliver the intervention. All courses were audio recorded and a random selection of the recordings of particular components from each course was analysed to evaluate intervention fidelity, described in detail elsewhere [30]. Participants present for at least 17 of the 24 course components were deemed 'adherent' to the intervention according to pre-determined criterion.

Table 1 Outline of the intervention – The COPERS course

Day	Modules	Content of sessions
1 Living and dealing with pain	1. Introduction and Understanding pain and acceptance	Session 1: Introduction Session 2: Pain information Session 3: Acceptance: The uninvited guest
	Lunch	
	Taster activity – Art	
	2. Mind, mood and pain	Session 4: Pain, when is it bearable and when is it not? Session 5: The pain cycle
	3. Movement and Relaxation	Session 6: Posture Session 7: Relaxation and breathing
2 Doing something about your life with pain	4. Dealing with unhelpful, negative thoughts and barriers to change	Session 8: Reflections from day one Session 9: Identifying problems, goal setting and action planning Session 10: Barriers to change - unhelpful thinking
	Lunch	
	Taster activity – Hand massage	
	5. Making pain more manageable	Session 11: Barriers to change – reframing negatives to positives Session 12: Attention control and distraction Session 13: Things that make pain more manageable
	6. Movement and Relaxation	Session 14: Balance and stretch Session 15: Relaxation and visualisation
3 Communication and relationships	7. Communication skills	Session 16: Reflections from day 2 Session 17: Communicating with your GP Session 18: Listening skills Session 19: Anger, irritability and frustration
	Lunch	
	Taster activity – Volunteering	
	8. Movement and Relaxation	Session 20: Stretch Session 21: Relaxation and mindfulness of thoughts Session 22. Summary of the course
4 Follow up	9. The future	Session 23: Reflections and feedback from the group Session 24: Managing setbacks

Usual care

The control group received usual care, including a widely available pain education leaflet (http://www.paintoolkit.org/downloads/SC_TK_NHS_TAYSIDE.pdf), and a relaxation CD (also given to intervention participants). To mimic the duration of the intervention, control participants were asked to practise relaxation daily for three weeks and whenever they wished thereafter.

Statistical Analyses

To show a standardised mean difference (mean difference divided by the standard deviation at baseline) in pain related disability of 0.3 between intervention and control groups, at a 5% significance level with 80% power, would require data from 350 participants. To minimise the overall sample size in a situation where clustering occurred only in the intervention arm (due to the group intervention), we used Moerbeek's method, inflating the sample size by 1.37 (assuming an intra-cluster correlation coefficient of 0.1 and nine participants per course providing 12 month follow-up data) and using an unbalanced randomisation (1.33:1 in favour of the intervention) [31].We required data from 480 individuals. Allowing for a 30% loss to follow-up we sought to randomise 685 participants (391:294).

All analyses were performed according to the intention-to-treat principle. All participants with an available outcome were analysed according to the group to which they were randomised. All analyses accounted for clustering by course in the intervention arm through use of a random-effect in a mixed-effects regression model (with participants in the control arm acting as their own cluster) [32]. Treatment group, age, gender, site of recruitment (London or Midlands)[33-35], and baseline level of outcome were included in each analysis as fixed effects [36].

We used multiple imputation for analysis of the primary outcome of pain related disability [34]. We imputed the individual questions that formed the CPG disability score, and therefore included in the imputation

model and in the analysis all participants who answered at least one question on the CPG disability subscale at either 6 or 12 months. Participants who did not answer any questions on the CPG subscale at either 6 or 12 months were excluded from the analysis. We used multilevel imputation, with course included in the imputation model as a random effect. The imputation model included the three questions that formed the CPG disability score at baseline, 6 and 12 months, as well as site of recruitment, age, gender, HADS depression score at baseline, and employment status. Imputation was conducted separately within each treatment group, and 20 imputations were performed (i.e. we created 20 complete datasets). We analysed outcomes at 6 and 12 months separately, using a mixed-effects linear regression model as described above. Results were combined using Rubin's rules [37] Analysis of secondary outcomes is described in Section 4 of S1 Appendix.

We performed sensitivity analyses to assess robustness to different assumptions regarding the missing data (methods described in Section 5 of S1 Appendix). We performed the following pre-planned subgroup analyses for the primary outcome (full details in Section 11 of S1 Appendix): number of co-morbidities, living arrangements, baseline PSEQ score, socioeconomic status, pain duration, baseline CPG pain intensity score, baseline CPG disability score, and baseline HADS depression score. Subgroup analyses were performed by including an interaction between the specified subgroup and treatment arm in the analysis. Full details of the statistical methods can be found in the analysis plan (including details for all subgroup analyses, sensitivity analyses, and analyses of secondary outcomes) [17], which was finalised before any investigators had unmasked access to trial data. All analyses presented here were predefined in the statistical analysis plan [17] unless otherwise stated. A list of deviations from the analysis plan is available in Section 6 of S1 Appendix. Analysis was performed using Stata v13 and REALCOM [38].

Health economic analysis

The health economic analysis took a health-care provider perspective and estimated the costs of delivering the intervention and all further primary, secondary and community care costs (see Section 7 of S1 Appendix

for more detail on methods). Service use data, including all prescribing data, were collected from participants' GP electronic records at 12 months follow-up. Data relating to secondary care use over was downloaded from the Secondary Uses Services database [39]. Resource use data were combined with unit costs to calculate the total cost of health service use for each participant (see Section 8 of S1 Appendix for unit costs). Missing data for costs and Quality Adjusted Live Years (QALYs) were imputed using Stata 12.1.The primary economic analysis was a cost-utility analysis over 12 months using QALYs calculated from the EQ-5D-3L. We used a mixed-effects linear regression model to adjust estimates of costs and QALYs for: baseline measures, treatment group, age, gender, and site of recruitment as fixed effects and course as a random effect (with participants in the control arm acting as their own cluster). We used the non-parametric bootstrap and multiple imputations to compute cost-effectiveness acceptability curves and assessed cost-utility using willingness to pay thresholds ranging between £0 and £30,000 ($44,183). Costs were converted to US Dollars using purchasing power parity rate (2013) (http://stats.oecd.org/).

Results

Study participants

Between August 1, 2011 and July 31, 2012 we randomised 703 participants from 35 general practices, two secondary care pain services and one community based musculoskeletal service (403:300, intervention: control) (Fig I).

----------Insert Fig 1 COPERS Consort Flow chart here----------

We over recruited to ensure the final self-management support groups at all study centres achieved the pre-specified minimum number of attending participants (five). Intervention and control participants were well matched at baseline (Table 2). Most of the participants (85%) had had pain for at least three years with 265 (38%) reporting pain for more than ten years and 162 (23%) being prescribed strong opioids (as defined in the British National Formulary [40]) at baseline. The median number of co-morbidities (determined from primary care records) was two (range 0-8). Only 169 (24%) were in any form of employment, with 148 (21%)

191 unable to work due to long term sickness and another 307 (44%) who were retired. Overall health utility as
192 assessed by the EQ-5D-3L (commonly interpreted as quality of life) was very low (mean 0.4, SD 0.34).
193
194 Eleven health care professionals and 13 lay people delivered 35 courses (the mean number of participants
195 per course was 14). The mean waiting time from randomisation to attending a course was six weeks (range
196 0-24 weeks); 67/403 (17%) intervention participants did not attend a course, and 282 (70%) met our pre-
197 defined definition of adherence.

Table 2 Baseline characteristics

	Control *n=300* Number (%) unless indicated otherwise	**Intervention *n=403* Number (%) unless indicated otherwise**	**Number of Participants with missing data (control, intervention)**
Age (years) – mean (SD)	59.4 (13.8)	60.3 (13.5)	0, 0
Male	98 (33)	132 (33)	0, 0
Lives alone	101 (34)	143 (36)	4, 6
Ethnicity			0, 0
White	239 (80)	325 (81)	-
Black	36 (12)	53 (13)	-
Asian	20 (7)	13 (3)	-
Mixed/other	5 (<1)	12 (3)	-
Age at which formal education ended			0, 0
16 years old or less	157 (52)	224 (56)	-
20 years old or later	135 (45)	173 (43)	-
Other	8 (3)	6 (1)	-
Employment status			0, 0
Employed, including self-employed (full or part time)[a]	95 (32)	115 (29)	-
Unemployed looking for work or unable due to long term sickness	72 (24)	106 (26)	-

	Control ***n=300*** **Number (%) unless indicated otherwise**	**Intervention** ***n=403*** **Number (%) unless indicated otherwise**	**Number of Participants with missing data (control, intervention)**
Retired from paid work	132 (44)	175 (43)	-
Other	1 (<1)	7 (2)	-
Time kept from usual activities due to pain in past 6 months			3, 3
0-6 days	84 (28)	136 (34)	-
7-14 days	49 (17)	72 (18)	-
15-30 days	57 (19)	71 (18)	-
31 or more days	107 (36)	121 (30)	-
State of health[b]			0, 0
Very good	17 (6)	27 (7)	-
Good	100 (33)	138 (34)	-
Fair	130 (43)	159 (39)	-
Bad	45 (15)	63 (16)	-
Very Bad	8 (3)	16 (4)	-
Duration of pain			0, 0
0-3 months	4 (1)	1 (<1)	-
4-12 months	10 (3)	15 (4)	-
13 months – 2 years	43 (14)	45 (11)	-
3-4 years	45 (15)	55 (14)	-
5-6 years	40 (13)	49 (12)	-
7-10 years	50 (17)	81 (20)	-
More than 10 years	108 (36)	157 (39)	-
CPG[20] overall[c]			3, 5
0	0 (0)	0 (0)	-
1	18 (6)	30 (8)	-

	Control ***n=300*** **Number (%) unless indicated otherwise**	**Intervention** ***n=403*** **Number (%) unless indicated otherwise**	**Number of Participants with missing data (control, intervention)**
2	66 (22)	99 (25)	-
3	81 (27)	123 (31)	-
4	132 (44)	146 (37)	-
CPG[20] disability[d] – mean (SD)	63.8 (24.4)	62.9 (25.7)	0, 1
CPG[20] pain intensity[e] – mean (SD)	70.9 (15.3)	71.5 (17.0)	1, 1
PSEQ[29,f] – mean (SD)	30.6 (14.1)	31.2 (13.8)	0, 5
CPAQ[26, g] – mean (SD)	55.3 (19.1)	57.5 (20.7)	7, 15
HADS depression[25, h] – mean (SD)	7.5 (4.0)	7.4 (4.2)	3, 2
HADS anxiety[25, i] – mean (SD)	9.3 (4.7)	9.2 (4.6)	3, 3
HADS[25] depression score categories			3, 2
0 – 7 (normal)	159 (54)	217 (54)	
8 – 10 (mild)	74 (25)	95 (24)	
11 – 21(moderate or severe)	64 (22)	89 (22)	
Health education impact questionnaire (heiQ)[27]Social integration and support subscale[j]– mean (SD)	13.8 (3.4)	14.0 (3.6)	5, 3
EQ-5D-3L[28,k]– mean (SD)	0.39 (0.34)	0.41 (0.34)	1, 1
Number of co-morbidities[l] – median (IQR)	3 (2 to 4)	2 (2 to 3)	21, 32

[a] Includes in full time education and looking after home/ family [b]UK Census general health question[24], [c]CPG Pain grades 0 (no pain)- 4(high disability, severely limiting pain);[d]CPG pain disability, mean CPG disability items scored on a scale 0-10 (worst) and multiplied by 100 thus 100 = worst possible score; [e]CPG pain intensity, mean of the three pain intensity CPG items scored on a scale 0-10 (worst)and multiplied by 100; [f]PSEQ 0-60 (best);[g]CPAQ 0-120(best), [h]HADS depression0-21 (worst), [i]HADS anxiety0-21 (worst);[j]HEIQ4-20 (best),[k]EQ5D<0-1 (best),[l] from primary care records.

198 ***Pain related disability***

We obtained a complete set of baseline and primary outcome data from 621 (88%) participants, with multiple imputation for missing primary outcome data (see above) were able to include 652 (93%) participants in our analysis (Figure 1). Table 3 shows the results for primary and secondary outcomes at six and 12 months follow-up. Pain related disability did not differ between treatment groups at either time (12 months: intervention mean 52.9 (SD 28.0) vs. control mean 53.3 (SD 28.8); difference (intervention vs. control) -1.0, 95% CI -4.9 to 3.0).

Table 3. Main results for primary and secondary outcomes

	Control[a] ***(n=300)***	**Intervention[a]** ***(n=403)***	**Treatment effect[b] (95% CI)**	
	Mean (SD)	**Mean (SD)**	**Difference in means (intervention minus control)**	**SMD[c] (standardised mean difference)**
Chronic Pain Grade[20] CPG disability				
6 months	54.3 (26.7)	53.2 (25.7)	-1.2 (-4.8 to 2.4)	-0.06 (-0.24 to 0.12)
12 months	53.3 (28.8)	52.9 (28.0)	-1.0 (-4.9 to 3.0)	-0.04 (-0.22 to 0.13)
CPG pain intensity				
6 months	64.3 (19.4)	65.0 (18.8)	1.0 (-1.5 to 3.6)	0.07 (-0.10 to 0.24)
12 months	64.4 (20.1)	63.5 (20.3)	-0.9 (-3.7 to 1.9)	-0.06 (-0.23 to 0.12)
Pain self-efficacy Questionnaire[29] PSEQ score				
6 months	32.7 (15.0)	35.5 (14.0)	2.3 (0.6 to 4.1)	0.25 (0.07 to 0.43)
12 months	33.4 (15.1)	35.4 (14.1)	1.4 (-0.2 to 3.1)	0.15 (-0.02 to 0.32)
Hospital Anxiety Depression Scale[25]				

	Control[a] ***(n=300)***	**Intervention**[a] ***(n=403)***	**Treatment effect**[b] **(95% CI)**	
HADS Anxiety score				
6 months	9.1 (4.8)	8.2 (4.7)	-0.7 (-1.3 to -0.2)	-0.24 (-0.41 to -0.06)
	Mean (SD)	**Mean (SD)**	**Difference in means (intervention minus control)**	**SMD (standardised mean difference)**
12 months	8.4 (4.5)	8.1 (4.5)	-0.4 (-0.9 to 0.1)	-0.13 (-0.30 to 0.03)
HADS[25] Depression score				
6 months	7.0 (4.4)	6.3 (4.1)	-0.7 (-1.2 to -0.2)	-0.25 (-0.44 to -0.06)
12 months	6.9 (4.6)	6.2 (4.3)	-0.7 (-1.2 to -0.2)	-0.22 (-0.39 to -0.06)
Chronic Pain Acceptance Questionnaire[26] CPAQ score				
6 months	59.2 (19.7)	64.4 (20.0)	3.4 (1.3 to 5.5)	0.27 (0.08 to 0.45)
12 months	74.0 (14.4)	73.1 (15.1)	-0.8 (-3.0 to 1.4)	-0.03 (-0.20 to 0.13)
Health education impact questionnaire (heiQ)[27]Social integration and support subscale				
6 months	14.3 (3.6)	14.9 (3.3)	0.6 (0.1 to 1.0)	0.25 (0.06 to 0.43)
12 months	14.1 (3.6)	14.9 (3.5)	0.8 (0.4 to 1.2)	0.32 (0.16 to 0.49)
	Mean (SD)	**Mean (SD)**	**Difference in means**	**SMD (standardised mean difference)**

	Control[a] ***(n=300)***	**Intervention**[a] ***(n=403)***	**Treatment effect**[b] **(95% CI)**	
			(intervention minus control)	
EQ-5D-3L[28]				
6 months	0.41 (0.35)	0.46 (0.34)	0.03 (-0.01 to 0.08)	0.13 (-0.03 to 0.29)
12 months	0.45 (0.35)	0.46 (0.34)	0.00 (-0.04 to 0.04)	0.01 (-0.16 to 0.17)

[a]Mean (SD) for both treatment groups are based on raw data, i.e. are unadjusted.
[b] The difference in means and the SMD were adjusted for age, gender, site of recruitment (London or Midlands), and baseline level of outcome.
[c] SMDs were calculated using the residual SD obtained from the analysis model.

Secondary outcomes

At six months self-efficacy (PSEQ , difference 2.3, 95% CI 0.6 to 4.1), anxiety (HADS anxiety subscale, -0.7, 95% CI -1.3 to -0.2), depression (HADS depression subscale, -0.7, 95% CI -1.2 to -0.2), pain acceptance (CPAQ, 3.4, 95% CI 1.3 to 5.5) and social integration (heiQ, 0.6, 95% CI 0.1 to 1.0) had all improved more in the intervention group compared to the control group (Table 3). At 12 months the differences favouring the intervention were sustained for depression (-0.7, 95% CI -1.2 to -0.2) and social integration (0.8, 95% CI 0.4 to 1.2). All sensitivity analyses found similar results to the primary analysis, demonstrating that primary outcome results were robust (see Section 9 of S1 Appendix for full results).

There was no difference in responses to the Census global health question at 6 or 12 months follow up (odds ratio for intervention group participants being improved at 12 months was 1.07, 95% CI 0.77 to 1.51). Overall intervention patients received considerably more analgesics than controls in the 12 months following randomisation (amounting to an average difference of 98 days of medication at WHO standard dosing (95% CI 17 to 178)). They also received significantly more weak opioids (18 DDDs, 95% CI 5 to 32 days). However there was no evidence of any difference in the prescription of strong opioids between treatment arms (-1

DDD, 95% CI -12 to 11), nor in the proportions of those receiving strong opioids at 12 months (see Section 10 of S1 Appendix for full results).

No serious adverse events occurred with the intervention or in the control arm. Two deaths occurred during the study: one intervention patient and one control patient. Both cases were considered by the chair of our DMEC to be unrelated to the study and thus not to represent adverse events.

Pre-specified sub-group analyses, examining subgroups based on number of co-morbidities, living arrangements, baseline PSEQ score, socioeconomic status, pain duration, baseline CPG pain intensity score, baseline CPG disability score, and baseline HADS depression score, found no differences across subgroups (full results in Section 11 of S1 Appendix) for the primary outcome. An exploratory post hoc sub-group analysis found that improvement in 12 month depression scores occurred only in those who were likely to be depressed at baseline (P value for interaction 0.004) (Table 4). No serious adverse events occurred with the intervention or in the control arm.

Table 4 Sub-group analysis* of HADS depression score at 12 months by HADS depression score at baseline: 0-7 vs. 8-21

HADS depression score at baseline	Control – mean (SD)	Intervention – mean (SD)	Treatment effect (95% CI)	P-value for interaction
Original scale				
0-7	4.2 (3.0)	4.0 (3.0)	0.0 (-0.7 to 0.6)	0.004
8-21	9.4 (4.8)	8.2 (4.7)	-1.5 (-2.3 to -0.8)	
Standardised mean difference				
0-7	-	-	-0.01 (-0.23 to 0.21)	-
8-21	-	-	-0.50 (-0.74 to -0.25)	

*625 participants were included in the sub-group analysis: 348 patients with HADS depression score 0-7 (148 usual care, 200 intervention), and 277 patients with HADS depression score 8-21 (113 usual care, 164 intervention).

Health economic analyses

We obtained complete health economics data from 540 participants (77%) of participants. The highest proportion of missing data was for baseline prescriptions, followed by EQ-5D-3L and primary care contacts. Imputing the data for missing values resulted in a data set of 647 participants (92%) (control n=275, intervention n=372), which represented 99% of the trial population included in the statistical analyses of the primary outcome. The cost of delivering courses, including the cost of training the facilitators was £145 ($214) per person. Total costs were higher in the intervention group (£2,955, $4,352) compared to the control group (£2,767, $4,075) and the difference in means was £188 ($277), 95% CI -£125 (-$184) to £501 ($738). Total QALYs were also higher in the intervention group (0.4475) compared to the control group (0.4150) and the difference in the means was 0.0325 (95%CI -0.0074; 0.0724) QALYs. The ICER mean point estimate was £5,786 ($8,521) per QALY. The intervention had a high probability (87%) of being cost-effective at a willingness to pay of £30,000 ($44,183) per QALY. Results of cost-effectiveness analyses are shown in Section 12 of S1 Appendix.

Discussion

Our chronic pain self-management intervention (COPERS) was relatively cheap to deliver, and had a good uptake (336/403, 86%) with little attrition. We found no evidence of impact on our primary outcome of pain related disability at 12 months, or at six months. However at six months the COPERS intervention led to improved psychological well-being compared to the control group with regard to all our psychological measures - anxiety, depression, chronic pain acceptance and pain related self-efficacy. At 12 months the intervention arm showed continued beneficial effects on depression and social integration. These changes in health related quality of life were reflected in an incremental gain in QALYs of 0.035, a gain that was similar in size to that observed in other patient self-management programmes [41-42], and the intervention did not result in any adverse events. The intervention was also relatively low cost, resulting in a mean costs of £5,786 ($8,521) per QALY. There is uncertainty around the estimates of costs and QALYs but when we took account of this uncertainty the intervention was shown to have a high probability (87%) of being cost

effective at the current UK National Institute for Health and Care threshold of £30,000 ($44,183) per QALY [43].

The finding of a long term effect on the secondary outcome of depression is of some interest. Nearly half our participants 322/703 (46%) met the criterion for possible clinical depression at baseline [44].Our observed overall effect size on depressive symptoms exceeds the effect size found in an individual patient data meta-analysis of selective serotonin reuptake inhibitors for mild/moderate depression (SMD 0.11, 95% CI −0.18 to 0.41), or severe depression (SMD 0.17, 95% CI −0.08 to 0.43) [45].

An exploratory post-hoc analysis found a clinically significant, sustained, improvement in depressive symptoms at 12 months amongst participants with depressive symptoms at baseline; with no benefit for those who did not meet this criterion. In these post hoc analyses the SMD gain from our intervention in the group meeting the depression criterion (-0.50, 95% CI -0.74 to -0.25) is of a similar size to those reported in a network meta-analysis of large trials (≥50 per group) of psychotherapeutic interventions for depression [46]; Interpersonal therapy -0.73 (-1.14 to 0.32); cognitive behavioural therapy -0.47 (-0.80 to -0.35), or problem solving therapy -0.46 (-0.81 tp-0.12); and in that reported in a Cochrane review of tricyclic antidepressants in primary care (-0.49, 95% CI -0.67 to -0.32) [47]. Notwithstanding these promising results the COPERS intervention cannot be recommended for people with depressive symptoms associated with musculoskeletal pain without evidence that this effect is found in a study including only those with depressive symptoms.

The key strengths of this study were its pragmatic design, the lack of attrition and robustness of the results. We used multiple imputation to include all participants with follow-up data in the analysis, and conducted extensive sensitivity analyses to confirm the robustness of our results. Before we analysed the trial outcome we evaluated the fidelity of our intervention-this showed that it was delivered as intended [30].

All outcomes in both intervention and control groups improved over time (Tables 2 and 3). The inclusion of a relaxation CD and leaflet along with usual care in the control arm might have reduced the apparent effectiveness of the intervention. We chose the relaxation package because other studies had suggested that although relaxation was popular it was unlikely to have an effect on our primary outcome of pain related disability or have long term effects, but we cannot exclude the possibility that it had a therapeutic effect [15].

It not clear why participants in the intervention group were prescribed more pain killers than those in the control arm. This finding might have arisen as a result of their gaining greater confidence or skill in communicating with their health professionals (an explicit aim of the intervention). The COPERS intervention could be more effective if it was combined with an intervention which attempted to optimise analgesic prescribing for each individual (a strategy we are currently investigating in chronic headache http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/other/chess/).

A review and meta-analysis of mediation studies of people with back and neck pain found evidence that self-efficacy, psychological distress and fear (principally fear of movement) may explain the development of disability in people with low back or neck pain [48], although the studies were noted to be of low quality. In our study improvements in self-efficacy and psychological distress were *not* accompanied by a reduction in self-reported pain related disability. It is possible that our intervention was too brief to have an effect on pain outcomes in this population who, overall, reported a long history of pain, high levels of pain related disability and low quality of life at baseline; but we were able to demonstrate a sustained effect on psychological outcomes. Most psychological interventions recognise that while improvements in pain in these patients are unlikely, improving function and well-being are paramount. Our intervention performed as well as CBT for chronic pain [49].

Improving pain related disability may require more intensive exercise based interventions, whilst this intervention was devised to encourage behaviour change for long term lifestyle change. Using this type of intervention as an adjunctive treatment may be optimal, for example with a stepped care analgesic algorithm, as for example in the SCOPE trial [50].

Although this brief intervention appears to be inexpensive and safe, and had a good uptake and low attrition, it did not improve the primary outcome of pain related disability. The intervention's potential to improve the psychological wellbeing of people with chronic pain, many of whom may also be anxious or depressed, could potentially benefit large numbers of people with chronic pain, but requires further research. Currently it is difficult to justify its use for those without depression and we do not know its effectiveness if only people with probable depression are included in the groups.

Conclusion

This novel, theoretically based intervention did not improve pain related disability in people with chronic musculoskeletal pain. It may have a valuable role in promoting psychological well-being amongst people with chronic pain who are also anxious or depressed, but this needs further research. Moreover, effective interventions to improve hard to shift outcomes, such as disability, in chronic pain patients are still required.

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Disclaimer:
The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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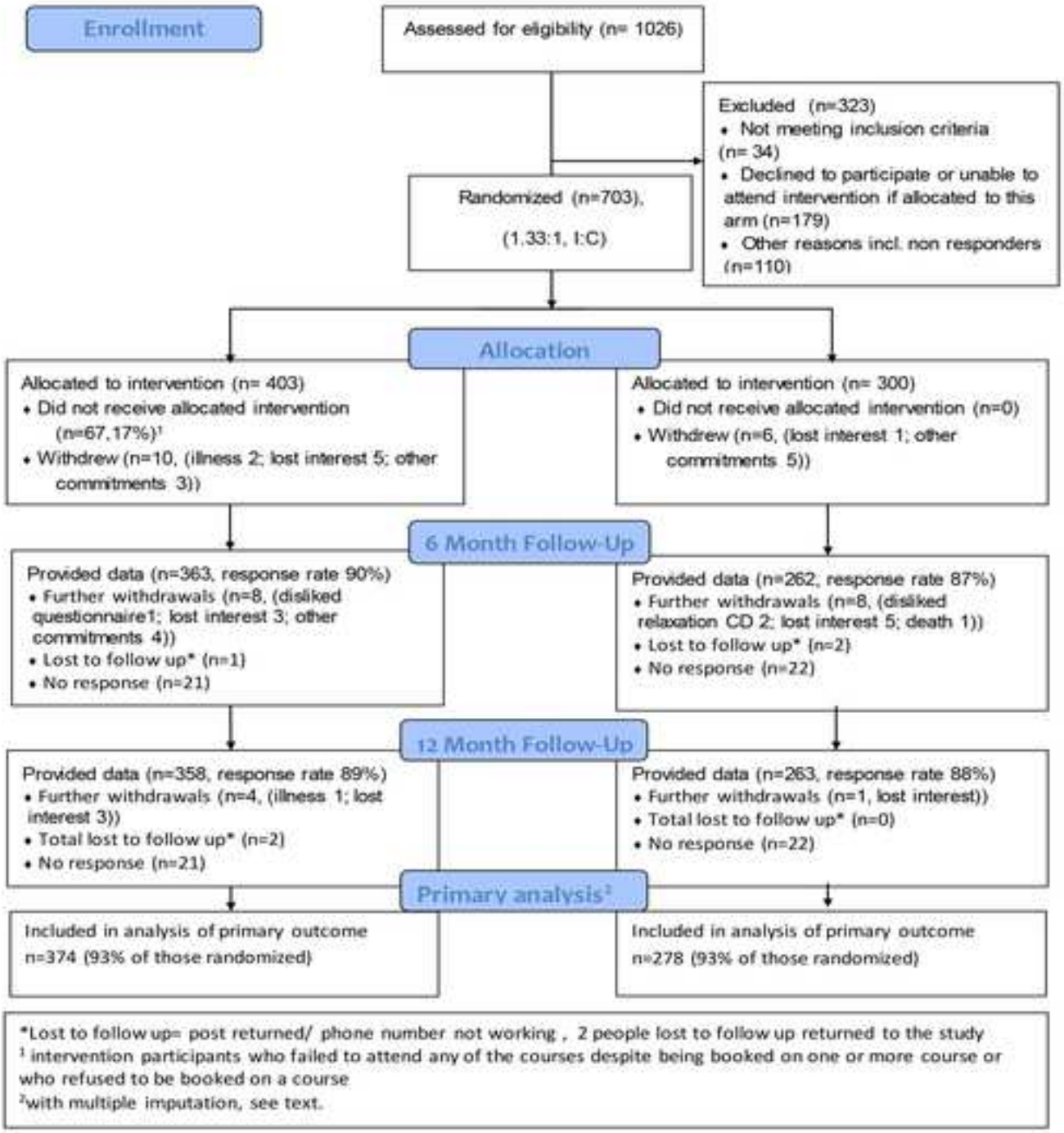
Supporting Information

S1_Appendix.pdf	Supplementary web appendices
S1_CONSORT_checklist.docx	CONSORT 2010 checklist of information to include when reporting a randomised trial
S1_COPERS_Main_trial_protocol_V11_7_9_11.pdf	COping with persistent Pain, Effectiveness Research for Self-management: a randomised controlled trial (protocol)
S1_REC Final Approval letter Main trial.pdf	Letter from National Research Ethics Service Cambridgeshire 4 Research Ethics Committee

S1 Fig

Click here to download Figure S1_Fig1.tif

Fig 1: COPERS Study CONSORT Flow Diagram



S1 Ethics approval letter

S1 Consort checklist